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Interaction between stress and the *BDNF* Val66Met polymorphism in depression: a systematic review and meta-analysis

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Abstract

Background: Major depression is a disabling psychiatric illness with complex origins. Life stress (childhood adversity and recent stressful events) is a robust risk factor for depression. The relationship between life stress and Val66Met polymorphism in the brain-derived neurotrophic factor (*BDNF*) gene has received much attention. The aim of the present work was to review and conduct a meta-analysis on the results from published studies examining this interaction.

Methods: A literature search was conducted using PsychINFO and PubMed databases until 22 November 2013. A total of 22 studies with a pooled total of 14,233 participants met the inclusion criteria, the results of which were combined and a meta-analysis performed using the Liptak-Stouffer z-score method.

Results: The results suggest that the Met allele of *BDNF* Val66Met significantly moderates the relationship between life stress and depression ($P = 0.03$). When the studies were stratified by type of environmental stressor, the evidence was stronger for an interaction with stressful life events ($P = 0.01$) and weaker for interaction of *BDNF* Val66Met with childhood adversity ($P = 0.051$).

Conclusions: The interaction between *BDNF* and life stress in depression is stronger for stressful life events rather than childhood adversity. Methodological limitations of existing studies include poor measurement of life stress.

Keywords: Stress, Life events, Childhood maltreatment, Childhood adversity, Child abuse, Depression, Brain-derived neurotrophic factor, *BDNF*, rs6265, Gene-environment interaction

Background

Major depression is a prevalent psychiatric illness that is associated with considerable morbidity and mortality [1]. Much research has been dedicated to uncovering its aetiology with mixed success. Environmental factors, such as childhood adversity [2,3] and stressful life events [4-6] have been associated with the onset and course of major depression. However, not everyone exposed to such adversity develops this illness or relapses [6]; this has led researchers to explore stress vulnerability factors, including interactions with genetic influences [7]. The brain-derived

neurotrophic factor (*BDNF*) gene has been implicated in stress vulnerability [8]. Both variation in this gene sequence and stress exposure influence expression and intracellular trafficking of the *BDNF* protein. Stress is hypothesised to cause a reduction in *BDNF* (protein) levels in the brain (particularly in regions linked to emotion), which alters mood and may cause depression [9]. Consequently, the *BDNF* gene has been identified as a stress vulnerability candidate generating much research, which has yet to be reviewed or synthesised.

The purpose of the present work was to systematically review and perform a meta-analysis on studies that have investigated the interaction between the Val66-Met polymorphism in the *BDNF* gene and life stress (childhood adversity and stressful life events) in depression.

Major depression has a lifetime prevalence of 17% [10] and is diagnosed based on the presentation of depressive

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symptoms (for example, low mood, sleep disturbance and suicidal behaviours) that last at least 2 weeks [1]. Depressive episodes are also experienced by individuals suffering from bipolar disorder, although the defining feature of this condition is mania (symptoms include, elation, grandiosity and irritability) [11].

Major depression is considered one of the most burdensome diseases in the world [12] and it is projected that this illness will be the second leading cause of disease burden for developed countries by 2020 [13]. Better understanding of the aetiology of this debilitating disorder is urgently required so that steps can be taken to reduce the burden on the individual, their families and society as a whole.

Life stress and depression

There is a wealth of literature concerned with the impact of life stress and depression, with studies focusing on childhood adversity and stressful life events.

Childhood adversity

Childhood adversity is defined as stressful experiences that occur early in life; examples include abuse (such as sexual and physical abuse), neglect (failure of caretakers to provide the child with basic needs such as food or support), parental death and divorce. Significantly higher rates of childhood adversity are reported by adults with major depression compared to the general population [14]. Childhood adversity is also associated with worse course of depression, including lack of treatment response as well as more chronic and more frequent episodes [15].

Most studies in this area rely on retrospective reporting which is associated with various biases calling into question the validity and reliability of their findings. A recent study showed that whether childhood maltreatment is assessed prospectively (child protection database) or retrospectively (self-report), it is still significantly associated with major depression to a similar degree [16]. Moreover, Widom and colleagues [17] prospectively followed children who were abused or neglected (identified through court records), and found that as adults these individuals were at increased risk of major depression compared to matched controls.

Childhood adversity is a non-specific risk factor and has been linked to other emotional problems [18], psychiatric illnesses [16,19,20] and physical disorders [21,22]. A better understanding of the specific mechanisms that underlie the childhood adversity/depression association is needed.

Stressful life events

Stressful life events are described as circumstances that have a negative impact on an individual (for example, stress) that occur close to the onset or relapse of the illness [23]. Stressful events such as bereavement and divorce are common, but people's responses to such events vary, some appear to cope well and others spiral into a

depressive episode [6,24]. Although it has been shown that stressful life events cluster before a depressive episode or worsening of symptoms [4,25], there is strong evidence that one such event is sufficient to trigger an episode onset [26].

Investigating the relationship between stressful events and depression is not as straightforward as establishing whether an event occurred or not, various elements must be considered. Determining the direction of association is important, are stressful events generated by the individual and influenced by depressive symptoms (dependent events), or is it that such events occur 'out of blue' and trigger depressive episodes (independent events)? Establishing the event severity is essential as their impact differs between individuals and is dependent on circumstance. These key issues are addressed with the collection of contextual and biographical information best achieved using semi structured interviews [27-29]. Studies employing this method have consistently shown that severe independent events are linked to the onset, relapse and exacerbation of depressive symptoms [5,25,30], illustrating a causal relationship.

There is strong evidence for an association between life stress and depression, research now focuses on identifying stress vulnerability factors in depression including genetic factors [31,32].

Gene/environment interactions

Genetic sensitivity to one's environment or gene-environment interactions [33], has spurred much mental health research following Caspi and colleagues' [31] study. Their results showed that the low expressing short allele of the serotonin-transporter-linked promoter region polymorphism (*5-HTTLPR*; a functional variant in the serotonin transporter gene) increased depressive symptoms, rates of diagnosed depression and suicidality following exposure to stressful events and childhood maltreatment [31].

Many studies that attempted to replicate these results adopted different designs using divergent samples/populations, which resulted in mixed success [34,35]. The reviews [7,28,36] and meta-analytic studies [15,37] published on this topic suggest that the interaction is strongest between *5-HTTLPR* and childhood adversity, rather than recent stressful events [37]. Life stress assessment is crucial, with studies that used objective measures or semi structured interviews rather than crude self-report questionnaires detecting the interaction with the *5-HTTLPR* variant [37]. The relationship between life stress and the serotonin transporter gene is fairly consistent for persistent and recurrent depression [14,38,39].

Other genes have been implicated in stress vulnerability including the *CRHR1* [40,41], *FKBP5* [42] and *BDNF* [43] genes. The relationship between the Val66Met variant in the *BDNF* gene and stress in depression has been widely

researched and thus a systematic review and meta-analysis is warranted to synthesise the literature.

BDNF and life stress in depression

BDNF is a protein involved in the proliferation, differentiation and survival of neuronal cells and regulation of synaptic plasticity and connectivity in the adult brain [44]. Research suggests that BDNF may also be influential in sensitivity to stress.

According to the 'neurotrophic hypothesis' of depression [8,45], stress reduces BDNF activity, which results in decreased function in limbic brain regions (for example, hippocampus) involved in emotion processing and cognition. This reduction in turn is posited to be associated with depressed mood; while antidepressant therapy is hypothesised to reverse this effect [9,45]. There is evidence that stress and trauma result in decreased BDNF levels in both rodents [46,47] and humans [48,49]. The findings from several meta-analyses show that lower serum BDNF levels are detected among depressed patients relative to controls but these levels are normalised with antidepressant treatment [50,51]. There is some debate surrounding the link between BDNF, antidepressants and (hippocampal) neurogenesis (see [52] for more a detailed discussion). Together the evidence presented generally supports the 'neurotrophic hypothesis' of depression.

A single nucleotide polymorphism (SNP) in the *BDNF* gene (that is, Val66Met; rs6265) has been shown to influence the activity of the BDNF protein. This SNP results in the substitution of valine (Val) to methionine (Met) [53]. Although the *BDNF* gene consists of several polymorphisms many are in high linkage disequilibrium and highly correlated [54,55].

The Met allele of the *BDNF* Val66Met polymorphism has been linked with reduced BDNF activity [44], memory impairment [56] and harm avoidance [57]. Individuals with at least one Met allele of this SNP and at high risk of affective disorders (co-twin diagnosed with a mood disorder) have elevated evening cortisol levels, which suggests altered stress response [58].

Transgenic mice that are Met carriers of *BDNF* Val66Met exhibit increased anxiety-related behaviours under stress conditions [59], as well as decreased BDNF levels in the hippocampus [60], in line with the 'neurotrophic hypothesis'.

The research highlighted thus far presents a case for a significant interaction between *BDNF* Val66Met and life stress in depression. The purpose of the current paper is to systematically review and meta-analyse the literature concerned with this interaction addressing the specific question: 'is there a significant interaction between the Met variant of *BDNF* Val66Met and life stress in depression?'

Methods

Data sources and search strategy

The systematic review was performed according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines [61]. The literature searches were undertaken using PsychINFO, and PubMed up until 22 November 2013 for original research studies. The search terms were synonyms for depression, life stress and the *BDNF* Val66Met polymorphism (see Table 1). These terms were searched for in the articles' titles, keywords, tests and measures. Only papers published in the English language were considered for inclusion. The reference lists of identified studies were also searched by hand for relevant papers.

Eligibility criteria

The eligibility criteria were stipulated as follows: utilisation of human participants; depression (illness onset or relapse) or its symptoms were assessed; focus on *BDNF* Val66Met polymorphism (rs6265); childhood adversity and/or stressful life events (a range of types of events) were assessed; the interaction between stress and the *BDNF* Val66Met polymorphism was investigated. Studies in gross departure of Hardy-Weinberg equilibrium were excluded (for example, $P \leq 0.001$).

Data extraction

Variety of data were extracted from included studies in accordance with other gene-environment interaction reviews [37,62] (see Table 2). When publications reported results for both childhood adversity and recent stressful life events they were included in each environmental stressor group; but the results for each stressor were averaged and included in the overall analyses. The data was extracted and confirmed by two authors (GMH and KET). Where studies used multiple life stress and/or depression measures, the data yielded from interviews was included in the analyses. If the information required was not reported or unclear the authors of the original article were contacted.

Quality appraisal of studies

The methodological quality of included studies was evaluated against a quality checklist, derived from the STREGA ('Strengthening the Reporting of Genetic Association Studies') and STROBE ('Strengthening the Reporting of Observational Studies in Epidemiology') checklists [63,64], which have been used by other gene-environment interaction meta-analyses [37].

In accordance with current guidelines and previous reviews of gene-environment interaction studies [37], the studies were not weighted by quality scores or excluded based on low scores, but the information is presented in Additional file 1 for readers' evaluation.

Table 1 Terms used for literature search

| Keyword(s) | Additional search terms used |
|--------------------------------------|---|
| 1. Depression | Depressive disorder OR major depressive disorder OR depression OR major depression OR unipolar depression OR depressive symptoms |
| 2. Life stress | Stressful life events, OR life events OR negative life events OR adverse life events OR events OR stress OR stressors OR childhood maltreatment OR childhood adversity OR childhood stress OR child abuse OR child neglect OR adversity |
| 3. <i>BDNF</i> Val66Met polymorphism | Brain-derived neurotrophic factor gene OR <i>BDNF</i> OR rs6265 OR Val66Met |

Statistical analyses

The Liptak-Stouffer z-score method was used to combine studies at the level of significance tests with the results weighted by sample size. This approach has been used by another meta-analysis of gene-environment interactions [37]. This method involves a number of steps. First, the *P* values from the eligible studies were extracted and converted to one-tailed values, with those less than 0.50 indicating greater Met allele stress sensitivity and *P* values of greater than 0.50 corresponding to Val allele stress sensitivity in depression. Second, these *P* values were transformed into z-scores using a standard normal curve. Positive z-scores were assigned to *P* < 0.50 and negative z-scores corresponded to *P* > 0.50. Third, the z-scores were combined and weighted to take into account the study sample size. The following formula was used to do this:

$$Z_w = \frac{\sum_{i=1}^k w_i z_i}{\sqrt{\sum_{i=1}^k w_i^2}}$$

The weighting factor *w_i* corresponds to each study's sample size, *k* indicates the number of total studies, and *Z_i* corresponds to the z-scores of individual studies. *Z_w*, which is the outcome of this test, follows a standard normal distribution and thus related probability corresponds with a standard normal distribution table. This approach was used on the overall and stratified analyses.

Sensitivity analyses were undertaken to determine whether the results were considerably influenced by any single study; the procedure involved systematically excluding each study and recalculating the significance of the result.

To assess the potential impact of publication bias on the meta-analysis results the fail-safe *N* was calculated for all analyses. In line with Karg and colleagues [37], the number of studies with a *P* value equal to 0.50 and a sample size of 647 (average sample size of the studies analysed in the overall meta-analysis) were calculated that would need to be included in the weighted Liptak-Stouffer analyses to obtain a non-significant result. The ratio

between the fail-safe and the actual number of studies published provides an estimation of the possibility of publication bias effecting our findings.

Results

Study selection

A combination of the predefined search terms (depression + life stress + *BDNF* Val66Met) resulted in 1,019 hits; after duplicates were removed, 236 studies remained (see Figure 1). The abstracts of these articles were reviewed and those studies that reported on the interaction between life stress and *BDNF* Val66Met in depression were included. No existing systematic or meta-analytic reviews were found.

Overall evidence for *BDNF* × stress in mood disorders

Out of the 22 studies included, 8 reported a significant interaction between life stress (either life events or child adversity) and the Met variant of *BDNF* Val66Met in depression (see Table 2 and Figure 2).

Other studies provided partial evidence of a significant stress × *BDNF* for specific types of depression [65], childhood adversity [66,67] or detected a gender specific effect [68].

Several studies found a significant interaction between life stress and *BDNF* in depression using a Val recessive model [69-71]. The allele frequencies of the *BDNF* Val66Met polymorphism differs between ethnic groups, with the Met allele frequency highest among Asian populations [72]. Two of these studies used either a Han Chinese sample [69], or a cohort with mixed ethnicity [71], which may have contributed to the unusual finding with a Val recessive model.

Meta-analysis result

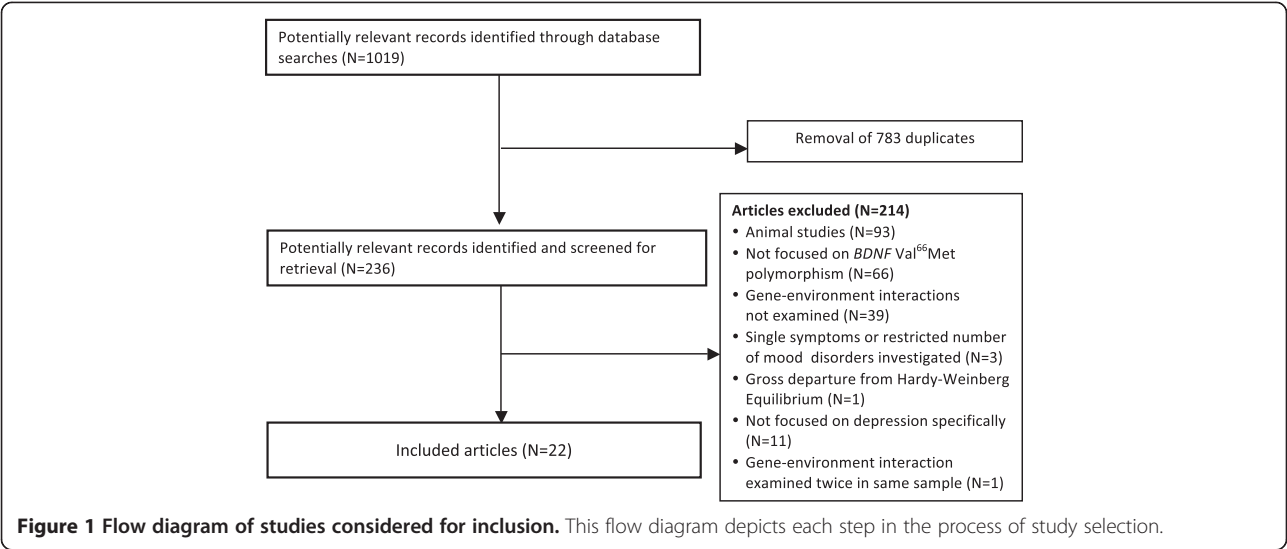
Combining the results from the identified studies with a total of 14,233 participants showed that the interaction between the Met variant of the *BDNF* Val66Met polymorphism significantly moderates the relationship between life stress and depression (*P* = 0.03). When findings from studies that used Caucasian samples were meta-analysed separately (to account for the potential confounding effect of population stratification), the results failed to reach conventional level of significance although they were in the expected direction (*P* = 0.07).

The sensitivity analyses showed that the results remained significant after removing each study in turn (>0.004 *P* < 0.049) with the exception of 4 studies [43,73-75]. In terms of publication bias, to make these results non-significant (*P* = 0.05), more than 11 unpublished or undiscovered studies with an average sample of 657 participants reporting a non-significant finding (*P* = 0.50) would need to exist. This corresponds to a fail-safe ratio of 2 studies not included in the meta-analysis for every included study.

Table 2 Summary of studies examining the interaction between life stress and brain-derived neurotrophic factor (BDNF) Val66Met in depression

| Source | N | Females,% | Age at study assessment (Mean or range) | Ancestry | Study design | Stressor | Life stress assessment | Outcome | Averaged one-sided P value |
|---|--------|-----------|---|------------------------------|-------------------------|---|---------------------------------------|---|----------------------------|
| Kaufman et al., 2006 [79] | 194 | 51 | 9.3 years | Mixed | Cross-sectional | Childhood adversity | Children taken into care | Depressive symptoms | 0.6765 |
| Kim et al., 2007 [43] | 732 | 59 | 65 years and over | East Asian | Cross-sectional | Stressful life events | Researcher-administered questionnaire | Depression diagnosis | 0.000315 |
| Wichers et al., 2008 [73] | 464 | 100 | 18 to 46 years | European | Longitudinal twin study | Childhood adversity | Questionnaire | Depressive symptoms | 0.009 |
| Aguilera et al., 2009 [66] | 470 | 55 | 22.9 years | European | Cross-sectional | Childhood adversity | Questionnaire | Depressive symptoms | 0.637 |
| Bukh et al., 2009 [82] | 290 | 66 | 38.5 years (median) | European | Case only | Stressful life events | Interview | Depression onset | 0.004 |
| Gatt et al., 2009 [88] | 374 | 51 | 36.2 years | European | Cross-sectional | Childhood adversity | Questionnaire | Depressive symptoms | 0.272 |
| Hosang et al., 2010 [75] | 1,085 | 62 | 37.83 years | European | Case-control | Stressful life events | Researcher-administered questionnaire | Bipolar disorder relapse | 0.02 |
| Lavebratt et al., 2010 [68] | 950 | 58 | 20 to 64 years | European | Longitudinal survey | Childhood adversity and Stressful life events | Questionnaire | Depressive diagnosis | 0.5 |
| Nederhof et al., 2010 [80] | 1,096 | 53 | 16.13 years | European | Longitudinal study | Childhood adversity | Questionnaires and interviews | Depressive symptoms | 0.3525 |
| Carver et al., 2011 [76] | 133 | 74 | 18.71 years | Mixed | Cross-sectional | Childhood adversity | Questionnaire | Depression diagnosis | 0.01 |
| Elzinga et al., 2011 [81] | 1,435 | 69 | 42.2 years | European | Case only | Childhood adversity and stressful life events | Interview | Depression diagnosis and symptom severity | 0.4325 |
| Juhász et al., 2011 [74] | 1,269 | 70 | 34.04 years | Caucasian | Cross-sectional | Childhood adversity and stressful life events | Questionnaire | Depression diagnosis | 0.13165 |
| Chen et al., 2012 [69] ^a | 780 | 51 | 13.6 years | Han Chinese | Longitudinal twin study | Stressful life events | Questionnaire | Depressive symptoms | 0.9875 |
| Grabe et al., 2012 [70] ^a | 2,035 | 53 | 55.6 years | Caucasian | Case only | Childhood adversity | Questionnaire | Depressive symptoms | 0.785 |
| Herbert et al., 2012 [83] | 279 | 100 | 36.8 years | Caucasian | Longitudinal study | Stressful life events | Interview | Depression diagnosis | 0.0935 |
| Perea et al., 2012 [77] | 302 | 50 | 18 years | Mixed (Columbian population) | Cross-sectional | Childhood adversity and stressful life events | Questionnaire | Depressive symptoms | 0.01725 |
| Quinn et al., 2012 [65] | 240 | 59 | 40.01 years | Unknown | Cross-sectional | Childhood adversity | Questionnaire | Melancholic subtype of depression diagnosis | 0.5 |
| Caldwell et al., 2013 [71] ^a | 124 | 66 | 21.97 years | Mixed | Cross-sectional | Childhood adversity | Questionnaire | Depressive symptoms | 0.8705 |
| Comasco et al., 2013 [67] | 1,393 | 50 | 17 to 18 years | European | Cross-sectional | Childhood adversity | Questionnaire | Depressive symptoms | 0.251 |
| La Greca et al., 2013 [78] | 116 | 54 | 8.85 years | Mixed | Cross-sectional | Childhood adversity | Questionnaire | Depressive symptoms | 0.167833 |
| Jiang et al., 2013 [89] ^a | 238 | 73 | 61.7 years | Caucasians | Cross-sectional | Stressful life events | Carer of person with dementia | Depressive symptoms | 0.9805 |
| Brown et al., 2013 [85] | 234 | 100 | 37 years | Caucasian | Longitudinal study | Childhood adversity and stressful life events | Interview | Depressive episode onset | 0.431 |
| Total | 14,233 | | | | | | | | |
| Average sample size | 647 | | | | | | | | 0.03 |

^aTested Val recessive model.



Since there is evidence for the differential interaction effect with child adversity and stressful life events with other SNPs (for example, *5-HTTLPR* [43]), the results pertaining to the impact of these types of stressors and the *BDNF* gene were examined.

Childhood adversity

In all, 16 studies explored the interaction between childhood adversity and *BDNF* in depression, 4 reported a significant effect [73,74,76,77] and 5 showed partial support for this interaction [65-68,78] (see Table 3).

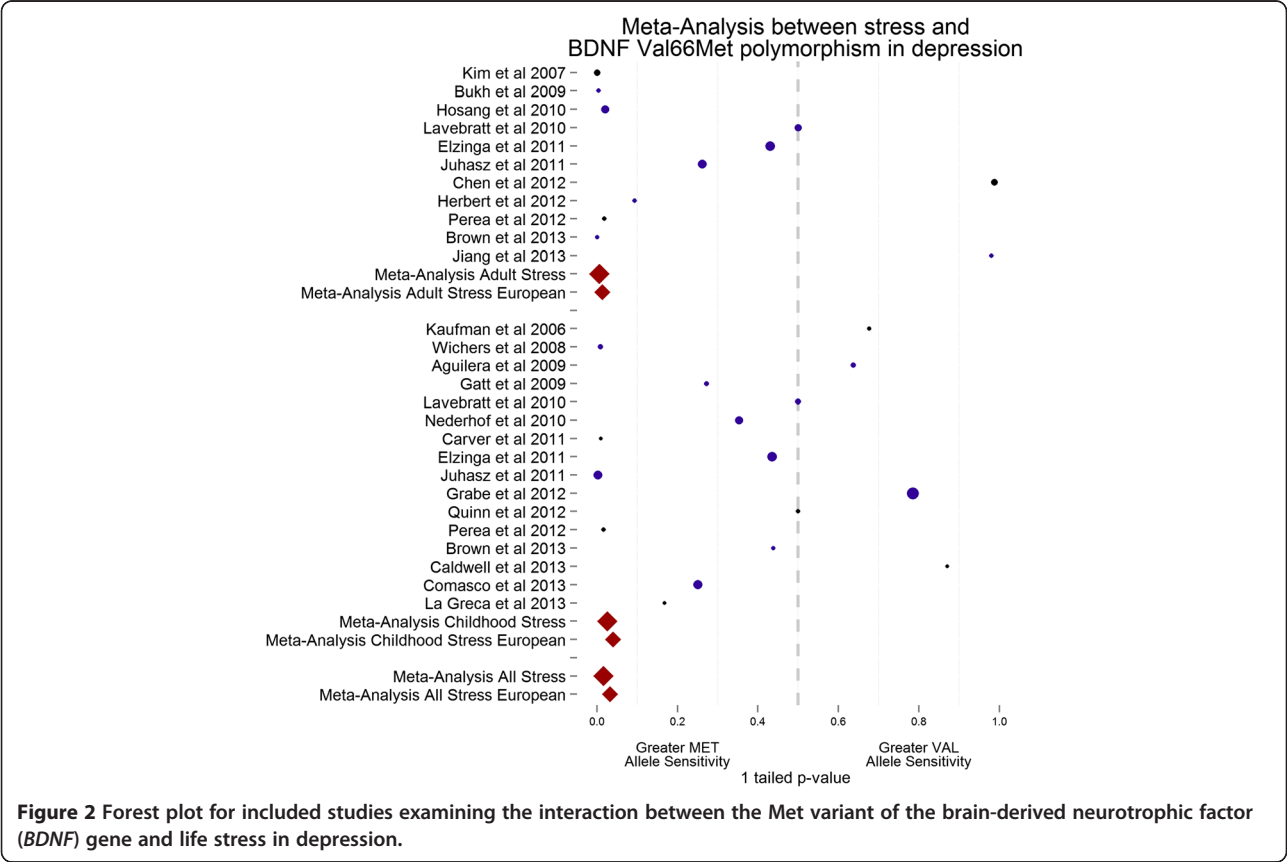


Table 3 Studies included in the childhood adversity meta-analysis

| Source | Sample size | One-sided <i>P</i> value |
|-----------------------------|-------------|--------------------------|
| Kaufman et al., 2006 [79] | 194 | 0.6765 |
| Wichers et al., 2008 [73] | 464 | 0.009 |
| Aguilera et al., 2009 [66] | 470 | 0.637 |
| Gatt et al., 2009 [88] | 374 | 0.272 |
| Lavebratt et al., 2010 [68] | 642 | 0.5 |
| Nederhof et al., 2010 [80] | 1,096 | 0.3525 |
| Carver et al., 2011 [76] | 133 | 0.01 |
| Juhasz et al., 2011 [74] | 1,269 | 0.0018 |
| Elzinga et al., 2011 [81] | 1,435 | 0.435 |
| Grabe et al., 2012 [70] | 2,035 | 0.785 |
| Quinn et al., 2012 [65] | 240 | 0.5 |
| Perea et al., 2012 [77] | 302 | 0.016 |
| La Greca et al., 2013 [78] | 116 | 0.167833 |
| Caldwell et al., 2013 [71] | 124 | 0.8705 |
| Comasco et al., 2013 [67] | 1,393 | 0.251 |
| Brown et al., 2013 [85] | 234 | 0.431 |
| Total | 10,521 | |
| Average sample size | 658 | 0.051 |

For instance, rather than investigating child adversity as one overarching construct, Aguilera and colleagues [66] focused on different types and only found a significant interaction between child sexual abuse and *BDNF*. Given the acknowledged heterogeneity in major depression [1], Quinn and associates [65] explored the impact of the child adversity-*BDNF* interaction on different subtypes of the disorder and found a significant effect for non-melancholic depression only.

The childhood adversity measures used by studies is particularly noteworthy, with all of the those reporting a significant interaction relying on questionnaires, while many of those studies not reporting an effect utilised more objective methods [79-81].

Childhood adversity: meta-analysis results

In meta-analysing the results from included studies with a combined sample of 10,521 individuals, a trend towards a significant interaction between childhood adversity and *BDNF* in depression was detected ($P = 0.051$), but was not improved on when only those studies with Caucasian samples were analysed ($P = 0.08$).

In undertaking sensitivity analyses, the results remained non-significant after removing each study in turn (>0.052 $P < 0.27$), with the exception of 6 [66,68,70,71,79,81].

Stressful life events

The stressful events-*BDNF* interaction in depression was investigated in 11 studies using a combined sample

of 7,594 individuals; 5 uncovered a significant effect (see Table 4). The majority of these studies used either researcher-administered questionnaires [43,75] or interviews [82], while the non-replicating studies relied on self-report checklists with one exception [83].

Bipolar disorder was the focus of one study [75], which found that the effect of stressful life events on episodes of bipolar depression were significantly greater in Met allele carriers (Met/Met and Val/Met) relative to those with the Val/Val genotype. However, no such pattern was reported for manic episodes [75].

Stressful life events: meta-analysis results

A significant interaction between stressful life events and the Met variant of *BDNF* Val66Met ($P = 0.01$) was found; the results remained significant when the analyses were restricted to studies using Caucasian samples ($P = 0.027$).

Sensitivity analysis showed the P value remained significant with the exclusion of each study from the analysis (>0.001 $P < 0.023$), except for 2 [43,75].

For this result to be non-significant ($P = 0.05$) more than 14 unpublished or unidentified studies need to exist with an average sample of 690 participants and a non-significant result ($P = 0.50$). This corresponds to a fail-safe ratio of 1 study not included for every study entered into the meta-analysis.

Discussion

A total of 22 studies with a combined sample of 14,233 participants met the eligibility criteria, 8 of which reported a significant interaction between life stress and the Met variant of *BDNF* Val66Met. The overall meta-analysis found evidence for a significant interaction between life stress and *BDNF* in depression using a Met dominant

Table 4 Studies included in the stressful life events meta-analysis

| Source | Sample size | One-sided <i>P</i> value |
|-----------------------------|-------------|--------------------------|
| Kim et al., 2007 [43] | 732 | 0.000315 |
| Bukh et al., 2009 [82] | 290 | 0.004 |
| Hosang et al., 2010 [75] | 1,085 | 0.02 |
| Lavebratt et al., 2010 [68] | 950 | 0.5 |
| Juhasz et al., 2011 [74] | 1,269 | 0.2615 |
| Elzinga et al., 2011 [81] | 1,435 | 0.43 |
| Chen et al., 2012 [69] | 780 | 0.9875 |
| Perea et al., 2012 [77] | 302 | 0.0185 |
| Herbert et al., 2012 [83] | 279 | 0.0935 |
| Jiang et al., 2013 [89] | 238 | 0.9805 |
| Brown et al., 2013 [85] | 234 | 0.0004 |
| Total | 7,594 | |
| Average sample size | 690 | 0.01 |

model. When the analyses were stratified by type of stressor, the results were strongest for stressful life events while the effect of childhood adversity failed to reach conventional levels of significance.

These findings help build a lifespan model of causation for major depression focusing on several gene-stress interactions. Research shows that childhood adversity (distal and stable risk factor) significantly interacts with the short allele of the 5-HTTLPR [37], while the findings from this meta-analysis suggest that the stressful life events (proximal and provoking factor) significantly interacts with the Met variant of *BDNF* in depression.

It has also been postulated that individuals who are genetically sensitive to adverse experiences (for example, Met carriers) may benefit most from positive environments or even the lack of adversity, under the 'differentially susceptibility' hypothesis [84]. One study [85] found that the likelihood of experiencing a depressive episode was significantly reduced among individuals with at least one Met allele of *BDNF* but only in the absence of a severe stressful event. It is possible that interventions that focus on providing supportive and positive environments would be most beneficial to individuals who are genetically sensitive to stress.

The aetiology of psychiatric disorders such as major depression is complex and is likely to involve multiple interactions between genetic variants and environmental factors. Few studies have explored the three-way interaction between childhood adversity, stressful life events and stress vulnerability genetic variants [86]. A wealth of research shows that adversity in childhood sensitises individuals to adult stressful life events increasing their risk for major depression [87]. Given the mounting evidence that genetic variants such as *BDNF* Val66Met polymorphism are important stress vulnerability factors sets the stage for future studies that should explore the childhood adversity \times stressful life events \times *BDNF* interaction in the context of depression.

Child adversity

When examining the specific influence of child adversity, 4 out of 16 studies reported a significant interaction with *BDNF* Val66Met for depression, and 5 were able to provide partial support for this interaction [65-68]. However, the results from the meta-analysis of these studies provided only a trend towards a significant effect.

On closer inspection of these results it appears that the childhood adversity-*BDNF* relationship in depression may be complex, with some studies reporting a significant interaction among women and not men [68,73], and for specific subtypes of depression (non-melancholic) [65]. In addition, specific forms of childhood adversity may be driving these associations (for example, child sexual abuse [66]). More research in this area is warranted focusing on specific forms

of adversity and depression subtypes as well as investigating gender differences.

The non-replicating studies have two characteristics that are noteworthy. Firstly, some studies which failed to detect any evidence for a child adversity \times *BDNF* in depression used child and adolescent cohorts [79,80]. Secondly, more reliable (for example, interviews [80,81]) and objective measures [79] of childhood adversity were adopted by these studies in comparison to those which found evidence for a gene-environment interaction who mainly used questionnaires (for example, [74,76]). There are several possible explanations for these null findings. The interaction between child adversity and *BDNF* may be developmentally sensitive and only manifests later in life (beyond adolescence). It is also possible that the *BDNF*-childhood adversity relationship in depression is a measurement artefact. Thus, future studies should assess an adult sample using interviews or objective measures of child adversity.

Stressful life events

The results of the meta-analysis showed that the effect of stressful life events on depression is significantly moderated by the *BDNF* polymorphism. The majority of the positive studies measured stressful events using researcher-administered questionnaires or interviews while the majority of the non-replicating studies utilised self-report checklists. It is possible that more objective and sensitive approaches to measuring stressful life events are required to observe its interaction with *BDNF* in depression.

BDNF

The *BDNF* gene consists of a number of polymorphisms which may also be relevant for gene-environment interactions in depression [55]. The majority of published studies have focused *BDNF* Val66Met, which allows for the present meta-analysis, but it would be useful for future studies to explore the relationship between other *BDNF* polymorphisms and stress in depression.

Limitations

The studies reviewed in this article are subject to a number of limitations. Firstly, different life stress measures were employed. Questionnaires present the biggest challenge as they rely on self-report and are vulnerable to various biases such as the participant's subjective interpretation of what counts as an event and enquire about a restricted number of events. Despite these limitations, most studies relied on self-report questionnaires, casting doubt on their results. Some studies have attempted to overcome these problems by using trained researchers to administer the questionnaires providing some improvement. More robust methods, such as life stress interviews or use of social services

records of child maltreatment are more objective and combat many of the biases associated with self-report.

Secondly, the majority of included studies used Caucasian samples, which may have influenced the results. It is possible that the *BDNF* × stress in depression is only relevant to Caucasian populations, although significant interactions have been reported among Asian [43] and ethnically mixed populations [76,77]. Future studies need to recruit participants from non-Caucasian backgrounds to test the generalisability of the *BDNF* × stress in depression to other ethnic groups.

Thirdly, several included studies may have limited power due to their restricted sample sizes (for example, [65,78]). For the current study, power analyses revealed that using the pooled samples provided greater than 80% power to detect significant effects of all three interactions tested in this project (these are, (1) life stress × *BDNF*, (2) childhood adversity × *BDNF*, (3) stressful life events × *BDNF* in depression).

Finally, the statistical approach used to conduct the current meta-analysis relied on combining the *P* values of existing studies, which were weighted by sample size. This approach was adopted to maximise the number of studies that could be included, with the aim of reducing biases associated with selecting a homogeneous set of studies and to better reflect the current evidence in this field. The meta-analytic method of combining *P* values could be improved upon by using traditional approaches that focus on combining effect sizes, which benefit from providing the magnitude of an effect.

Conclusions

A total of 22 studies with a pooled sample of 14,233 individuals were included in this review, of which 8 provided evidence in support of an interaction between life stress and the *BDNF* Val66Met polymorphism in depression. A meta-analysis provided evidence for an interaction between the Met variant of the *BDNF* Val66Met polymorphism and life stress in the causation of depression. When stratified by the type of stress, the results of the meta-analyses were only significant for stressful life events and not childhood adversity. This suggests that serotonin transporter and *BDNF* genes may confer sensitivity to early and late environmental factors respectively and play complementary yet distinct roles in the depression aetiology.

Additional file

Additional file 1: Table S1. Quality assessment of brain-derived neurotrophic factor (BDNF), life stress and depression studies [43,65-71,73-83,85,88,89].

Competing interests

GMH has provided sponsored talks for Bristol-Myers Squibb.

Authors' contributions

GMH was responsible for drafting the manuscript and collation of the data for analysis. KET undertook the analyses for the study, contributed to collation and checking the data. CS conducted the initial literature search and collation of data. RU and PMcG contributed to the design of the study and interpretation of the results. All authors were involved in drafting the manuscript and have given final approval of the version to be published.

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